Hier sei besonders Herrn Prof. Toyozo Uno für seine Unterstützung dieser Arbeit gedankt. Die Autoren danken auch dem Mikroanalytischen Laboratorium der Universität Kyoto für die Mikroanalysen und Herrn K. Machida und Frau I. Hamanaka für die Messungen der Infrarot-Spektren.

Zusammenfassung

Es wurden 2-Benzyliminomethyl-, 2-*p*-Methylbenzyliminomethyl-, 2-(1-Naphthyliminomethyl)-, 2-(2-Naphthyliminomethyl)-, 2-(*p*-Methoxybenzyliminomethyl)amin, 2-(*p*-Äthoxybenzyliminomethyl)-, 2-(*p*-Chlorbenzyliminomethyl)- und 2-(*p*-Brombenzyliminomethyl)pyrrol (abgekürzt Imine B) dargestellt. Ihre Reaktionen mit verschiedenen Metallen wurden mit den Reaktionen der in der ersten Mitteilung berichteten 2-Pyrrolylmethylenimine (abgekürzt Imine A) verglichen.

Die Kupferchelate sind dunkelblaue bzw. schwarze Kristalle, die in Chloroform und Äthylacetat leicht löslich und in Äthanol schwer löslich sind. Sie haben praktisch identische Absorptionsmaxima bei ca. 350 mμ in Äthylacetat. Ein Kupferchelat enthält Kupfer und Ligand im Verhältnis von 1 zu 2.

Imine B haben die C=N-Bande bei 1640 cm^{-1}, die sich bei Chelatkomplexbildung um ca. 50 cm^{-1} nach kleineren Frequenzen verschob. Es wurden auch N,N′-Bis(2-pyrrolyliden)äthylendiamin und sein Kupferchelat hergestellt, und auch hier haben die Autoren eine Verschiebung von 50 cm^{-1} wahrgenommen. Diese Ergebnisse zeigen, daß die Imino-Gruppe sich an der Chelatkomplexbildung beteiligt.

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UDC 547.92.07

70. Rinji Takasaki: Steroid Series. VII.*1 Synthesis of 6-Methyl-B-norsteroids.

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It is well known that the introduction of a methyl group in the 6-position of steroidal hormones results in strengthening of their hormonal action. In the previous papers of this series,[1],*1 new synthetic process was reported for B-norcholest-4-en-3-one, B-norpregn-4-ene-3,20-dione, and 17β-hydroxy-B-norandrost-4-en-3-one. Physiological action of these compounds are still being examined but it seemed of interest to prepare their 6-methyl derivatives and examine their physiological action at the same time.

It was reported in the previous papers[2] that ozone oxtdation of cholesterol acetate (Ia), 3β-hydroxypregn-5-en-20-one acetate (Ib), and 3β-hydroxyandrost-5-en-17-one acetate (If) at a low temperature and alumina chromatography of their products (IIa, b, f) afforded the corresponding B-nor-steroid derivatives (IIIa, b, f).accompanied with aldol condensation. In the present series of work. 6-methyl-B-nor-steroidal hormone analogs were synthesized by the use of (III) thus obtained.

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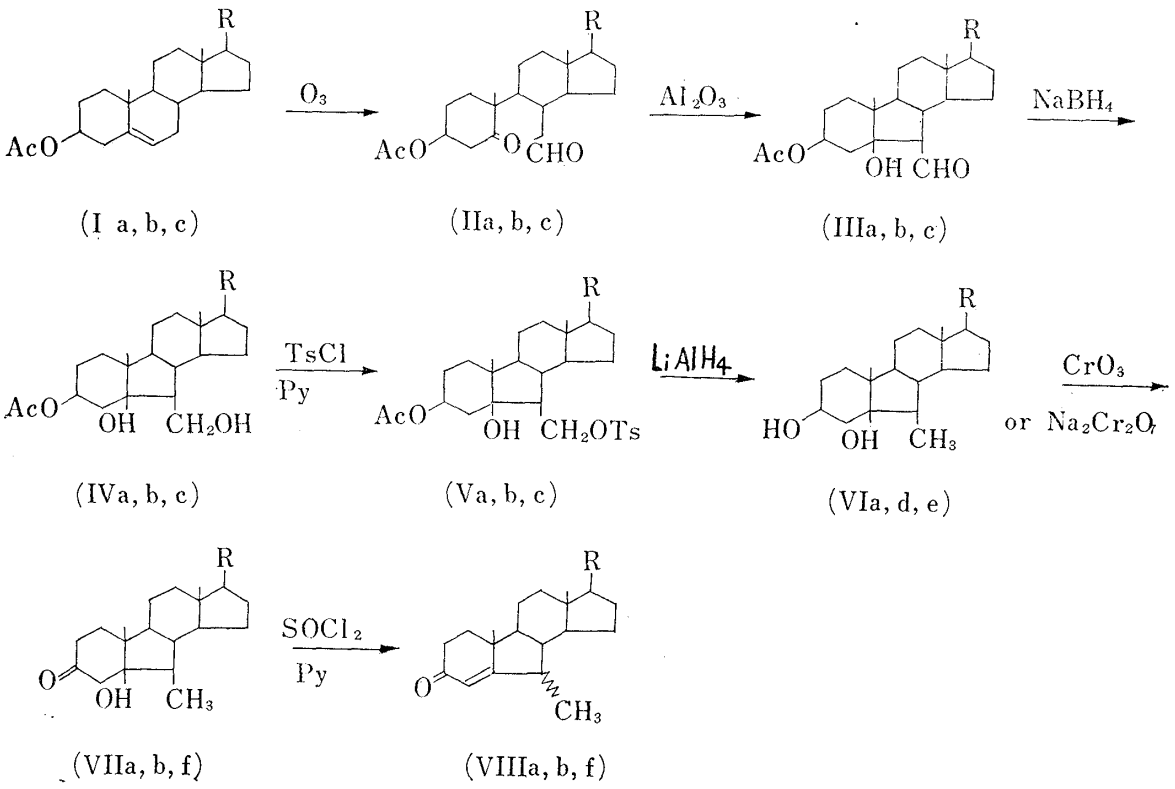
*1 Part VI: This Bulletin, **9**, 20 (1961).

*2 Nishi-shinagawa, Shinagawa-ku, Tokyo (高崎林治).

1) K. Tanabe, R. Hayashi, R. Takasaki: This Bulletin, **9**, 13 (1961).

2) *Idem*: *Ibid.*, **9**, 1, 7 (1961).



a : R=C_8H_{17} b : R=$COCH_3$ c : R=OAc d : R=$-CH(OH)-CH_3$

e : R=OH f : R=O

Reduction of 3β,5-dihydroxy-B-nor-5β-cholestane-6β-carboxaldehyde 3-acetate (IIIa) with sodium borohydride in methanol solution at room temperature affords 3β,5-dihydroxy-B-nor-5β-cholestane-6β-methanol (IVa), m.p. 91°, which forms a diacetate of m.p. 106° when acetylated by the usual method. This acetate was found to be identical with the product obtained by acetylation of a triol formed by reduction of methyl 3β,5-dihydroxy-B-nor-5β-cholestane-6β-carboxylate 3-acetate with lithium aluminium hydride. Treatment of (IVa) with tosyl chloride in pyridine gave a α-tosylate (Va), which did not crystallize. Treatment of (Va) with lithium aluminium hydride in ether gave 6β-methyl-B-nor-5β-cholestane-3β,5-diol (VIa), which melted at 85° after chromatography through alumina and recrystallization. This formed a monoacetate of m.p. 48~50°. Oxidation of (VIa) with chromium trioxide in acetic acid afforded 5-hydroxy-6β-methyl-B-nor-5β-cholestan-3-one (VIIa), m.p. 172°, whose infrared spectrum indicated absorption maxima at 3470 cm^{-1} (OH) and 1715 cm^{-1} (six-membered ring ketone). Treatment of (VIIa) with thionyl chloride in pyridine solution gave 6ξ-methyl-B-norcholest-4-en-3-one (VIIIa) which has absorption maximum at 239 mμ (ε 12,600) in the ultraviolet region, and absorption for 4-en-3-one group at 1663 cm^{-1} in its infrared spectrum. However, repeated chromatographic purification of (VIIIa) failed to effect its crystallization. Its semicarbazone, m.p. 234° (decomp.), showed ultraviolet absorption maximum at 270 mμ (ε 36,400), which agrees with the absorption for a semicarbazone of α,β-unsaturated ketone.[3]

The same series of reactions were carried out on pregnane and androstane series and the corresponding 6ξ-methyl-B-norpregn-4-ene-3,20-dione (VIIIb) and 6ξ-methyl-B-nor-

3) E. R. H. Jones, P. A. Wilkinson, R. H. Kerlogne : J. Chem. Soc., **1942**, 391.

androst-4-ene-3,17-dione (VIIIf) were synthesized. Reduction of 3β,5-dihydroxy-20-oxo-B-nor-5β-pregnane-6β-carboxaldehyde 3-acetate (IIIb) with sodium borohydride gave a tetrol monoacetate (IVd), which melted at 170~190° and is probably a mixture of 20α- and 20β-hydroxy isomers. Without further separation, this was submitted to tosylation with 1.1 moles of tosyl chloride in pyridine and the product was purified by chromatography through Florisil, from which a compound (Vd) of m.p. 154°, tosylated only at the primary alcohol, was obtained. It was revealed from the following experiments that this (Va) is 6'-monotosylate.

The triol, obtained by treatment of (Vd) with lithium aluminium hydride, forms a diacetate of m.p. 102°, and is oxidized by chromium trioxide into a substance of m.p. 193°, which is positive to Adachi's methyl ketone reaction[4] and shows absorption for acetyl at 1360 cm^{-1} in its infrared spectrum,[5] with overlapped strong absorptions for 6-membered ring ketone and 20-ketone group at 1710 cm^{-1}. It is cartain from these evidences that (VIIb) is 5-hydroxy-6β-methyl-B-nor-5β-pregnane-3,20-dione.

Treatment of (VIIb) with thionyl chloride in pyridine gives 6ξ-methyl-B-norpregn-4-ene-3,20-dione (VIIIb) of m.p. 113.5°, which showed absorption maxima at 240 mμ (ε 16,320) in its ultraviolet spectrum and at 1710 (20-CO), 1660, ane 1635 cm^{-1} (4-en-3-one) in its infrared spectrum.

Ozone oxidation of androst-5-ene-3β,17β-diol 3,17-diactate (Ic) in dichloro methane solution, reductive decomposition of the ozonide so formed with zinc and acetic acid, and alumina chromatography of its product gives as ubstance of m.p. 177~179° in 66.1% yield.*4 Its analytical values and infrared absorption maxima at 3530 (OH), 2770 (CHO), 1740 (AcO), and 1720 cm^{-1} (CHO) indicate that this substance is 3β,5,17β-trihydroxy-B-nor-5β-androstane-6β-carboxadehyde 3,17-diacetate (IIIc), formed from the intermediate 5-oxo-3β,17β-dihydroxy-5,6-secoandrostan-6-al diacetate (IIc) accompanying aldol condensation during the chromatography.[2]

Treatment of 3β,5,17β-trihydroxy-B-nor-5β-androstane-6β-methanol 3,17-diacetate (IVc). m.p. 177.5°, obtained by reduction of (IIIc) with sodium borohydride, with acetic anhydride in pyridine gives a α,3β,17β-triacetate of m.p. 123°. Tosylation of (IVc) and treatment of its product with lithium aluminium hydride gives 3β,5,17β-trihydroxy-6β-methyl-B-nor-5β-androstane (VIe), m.p. 92.5~94°, which was found to have 1.5 moles of water of crystallization from its analytical values.

Oxidation of (VIe) with chromium trioxide in acetic acid and treatment of its product, 5-hydroxy-6β-methyl-5β-androstane-3,17-dione (VIIf), m.p. 189°, with thionyl chloride in pyridine gives 6ξ-methyl-B-norandrost-4-ene-3,17-dione (VIIIf), m.p. 134°, which shows absorption maximum at 239.5 mμ (ε 15,900) in the ultraviolet region and absorptions at 1738 (17-CO), 1663, and 1635 cm^{-1} (4-en-3-one) in the infrared region.

The configuration of the 6-methyl group in all the compounds listed here is certain to be β-configuration, as in the starting material (III), with the exception of (VIIIa, b, f) from the nature of these chemical reactions. No conclusive evidence has been obtained on the configuration of 6-methyl group in (VIIIa, b, f).

Experimental*3

B-Norcholestane Series

3β,5-Dihydroxy-B-nor-5β-cholestane-6β-methanol 3-acetate (IVa)——A solution of 200 mg. of $NaBH_4$ in 10 cc. of MeOH and 5 drops of H_2O was added to the solution of 500 mg. of 3β,5-dihydroxy-B-nor-5β-cholestane-6β-carboxaldehyde 3-acetate (IIIa) dissolved in 20 cc. of MeOH and the mixture

*3 All m.p.s. are uncorrected. Optical rotation was measured in $CHCl_3$ solution.

*4 A convenient method for the preparation of the compound (III) will be reported in Part XI of the present series.

4) J. Adachi: Nippon Kagaku Zasshi, **71**, 560 (1950).
5) A. R. H. Cole: Fortschr. Chem. org. Naturstoffe, **14**, 44 (1956).

was stirred for 1 hr. Excess $NaBH_4$ was decomposed by the addition of AcOH, the solution was concentrated in a reduced pressure, and the residue was diluted with H_2O. This was extracted with Et_2O, the extract was washed with H_2O, dried over anhyd. Na_2SO_4, and Et_2O was evaporated. A small amount of hexane was added to the colorless syrupy product so obtained and the mixture was allowed to stand in a refrigerator, from which 430 mg. (85.6%) of 3β,5-dihydroxy-B-nor-5ξ-cholestane-6ξ-methanol 3-acetate (IVa) was obtained as columnar crystals, m.p. 88~89.5°. Recrystallization from the same solvent raised the m.p. to 90~91°. $[\alpha]_D^{28.5}$ +76.9° (c=2.14). *Anal.* Calcd. for $C_{29}H_{50}O_4$: C, 75.28; H, 10.89. Found: C, 75.01; H, 10.56. IR ν_{max}^{KBr} cm^{-1}: 3520~3400 (OH), 1737 (AcO).

3β,5-Dihydroxy-B-nor-5β-cholestane-6β-methanol α,3-Diacetate——A solution of 260 mg. of 3ξ,5-hydroxy-B-nor-5β-cholestane-6ξ-methanol 3-acetate (IVa) dissolved in 4 cc. of pyridine, added with 0.2 cc. of Ac_2O, was allowed to stand for 21 hr., poured into ice water, and extracted with Et_2O. The extract solution was washed consecutively with dil. HCl, dil. $NaHCO_3$, and H_2O, dried over anhyd. Na_2SO_4, and Et_2O was evaporated, leaving a colorless syrupy substance. Addition of MeOH effected crystallization and 200 mg. of crystals so obtained were recrystallized from MeOH to 3ξ,5-dihydroxy-B-nor-5ξ-cholestane-6β-methanol α,3-diacetate as cubic crystals, m.p. 105~106°, $[\alpha]_D^{26}$ +66.6° (c=1.44). *Anal.* Calcd. for $C_{31}H_{52}O_5$: C, 73.76; H, 10.38. Found: C, 73.35; H, 10.34. IR ν_{max}^{KBr} cm^{-1}: 3600 (OH), 1740 (AcO).

3β,5-Dihydroxy-B-nor-5β-cholestane-6β-methanol 3-Acetate α-Tosylate (Va)——A solution of 1.80 g. of tosyl chloride dissolved in 20 cc. of pyridine was added to a solution of 4.20 g. of (IVa) dissolved in 50 cc. of pyridine and the mixture was allowed to stand for 20 hr. at room temperature. This was poured into ice water, which was extracted with Et_2O and the extract was washed consecutively with dil. HCl, dil. $NaHCO_3$, and H_2O. After drying over Na_2SO_4, Et_2O was evaporated and 4.40 g. of a colorless syrupy substance thereby obtained was purified through Florisil chromatography but did not crystallize.

6β-Methyl-B-nor-5β-cholestane-3β,5-diol (VIa)——A solution of 4.4 g. of (Va) dissolved in 70 cc. of dehyd. Et_2O was added dropwise into a suspension of 1.2 g. of $LiAlH_4$ in 70 cc. of dehyd. Et_2O, with stirring, the mixture was refluxed for 20 hr., and cooled. Excess of the reagent was decomposed with AcOEt, the reaction mixture was acidified with 5% HCl, and extracted with Et_2O. The extract solution was washed with 2% $NaHCO_3$ and H_2O, dried over Na_2SO_4, and Et_2O was evaporated in a reduced pressure, leaving 3.0 g. of a colorless syrupy substance. This was chromatographed over 100 g. of alumina (Woelm grade II) and the fraction eluted with benzene-$CHCl_3$ (1:1) gave 1.826 g. (63.3%) of white crystals. Recrystallization from Me_2CO-M_2O afforded 6ξ-methyl-B-nor-5ξ-cholestane-3β,5-diol (VIa), m.p. 84~85°. $[\alpha]_D^{27}$ +55.7° (c=2.38). *Anal.* Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 79.98; H, 11.73. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3660, 3580 (OH).

6β-Methyl-B-nor-5β-cholestane-3β,5-diol 3-Acetate——A mixture of 200 mg. of (VIa) dissolved in 2 cc. of pyridine and added with 1 cc. of Ac_2O was allowed to stand for 20 hr. at room temperature, poured into ice water, and extracted with Et_2O. The extract solution was washed consecutively with dil. HCl, dil. $NaHCO_3$, and H_2O, dried over Na_2SO_4, and Et_2O was evaporated. The colorless oily residue thereby obtained was chromatographed over 10 g. of alumina (Woelm grade II) and benzene eluate afforded 6ξ-methyl-B-nor-5ξ-cholestane-3β,5-diol 3-acetate, m.p. 48~50°. *Anal.* Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 77.62; H, 11.21.

5-Hydroxy-6β-methyl-B-nor-5β-cholestan-3-one (VIIa)——A solution of 500 mg. of $Na_2Cr_2O_7 \cdot 2H_2O$ dissolved in 10 cc. of AcOH was added dropwise into a solution of 478 mg. of (VIa) dissolved in 10 cc. of AcOH, with ice cooling, the mixture was then allowed to stand for 3 hr. at room temperature, and excess of the reagent was decomposed by addition of MeOH. The solvent was evaporated, the residue was diluted with H_2O, and extracted with Et_2O. The extract solution was washed consecutively with H_2O, 2% $NaHCO_3$, and H_2O, dried over Na_2SO_4, and Et_2O was evaporated to leave ca. 500 mg. of yellowish brown solid. This residue was chromatographed over 15 g. of alumina (Woelm grade II) and the fraction eluted with benzene-$CHCl_3$ (20:1) afforded 247 mg. of white crystals. Recrystallization from MeOH gave 5-hydroxy-6β-methyl-B-nor-5ξ-cholestan-3-one (VIIa), m.p. 171-172°. $[\alpha]_D^{29.5}$ +1.6° (c=3.35). *Anal.* Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.77; H, 11.16. IR ν_{max}^{KBr} cm^{-1}: 3480 (OH), 1713 (3-CO).

6ξ-Methyl-B-norcholest-4-en-3-one (VIIIa)——To a solution of 650 mg. of (VIIa) dissolved in 8 cc. of pyridine and chilled to 0°, 0.5 cc. of $SOCl_2$ was added dropwise with stirring. After 10 min., the mixture was poured into ice water and extracted with Et_2O. The extract solution was washed consecutively with 5% HCl, H_2O, 1% $NaHCO_3$, and H_2O, dried over Na_2SO_4, and Et_2O was evaporated, leaving 320 mg. of a colorless syrupy substance. This residue was chromatographed over 15 g. of alumina (Woelm grade II) and the benzene eluate furnished 239 mg. of a colorless oily substance, which failed to crystallize. UV: λ_{max}^{EtOH} 240 mμ (ε 12,600). IR: $\nu_{max}^{CHCl_3}$ 1663 cm^{-1} (4-en-3-one).
Semicarbazone: Needles (from EtOH), m.p. 234° (decomp.). *Anal.* Calcd. for $C_{28}H_{47}ON_3$: N, 9.51. Found: N, 9.72. UV: λ_{max}^{EtOH} 270 mμ (ε 36,400).

B-Norpregnane Series

3β,5,20-Trihydroxy-B-nor-5β-pregnane-6β-methanol 3-Acetate (IVd)——To a solution of 8.0 g. of 3ξ-acetoxy-5-hydroxy-6ξ-formyl-B-nor-5ξ-pregnan-20-one (IIIb) dissolved in 320 cc. of MeOH, a solution of 3.2 g. of $NaBH_4$ dissolved in 160 cc. of MeOH (containing 10 cc. of H_2O), the mixture was stirred for 1 hr. at room temperature, and excess of the reagent was decomposed by addition of 10 cc. of AcOH. The solvent was distilled off in a reduced pressure, the residue was diluted with H_2O, and extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporation of Et_2O in a reduced pressure left 7.52 g. of white solid, m.p. 170~190°.

3β,5,20β-Trihydroxy-B-nor-5β-pregnane-6β-methanol 3-Acetate α-Tosylate (Vd)——To a solution of 7.2 g. of (IVd) dissolved in 75 cc. of pyridine and chilled to −10°, a solution of 4.3 g. of tosyl chloride dissolved in 35 cc. of pyridine was added dropwise, with stirring, during 1 hr., the mixture was stirred for further 1 hr. at −3° to −4°, and allowed to stand for subsequent 21 hr. at room temperature. This was poured into ice water, extracted with Et_2O, and the extract was washed consecutively with H_2O, 5% HCl, 2% $NaHCO_3$, and H_2O. After drying over Na_2SO_4, Et_2O was evaporated and 9.63 g. of an amorphous solid thereby obtained was chromatographed over 210 g. of Florisil. Elution with benzene and benzene-$CHCl_3$ (1:1) mixture furnished 4.385 g. (39.2%) of an amorphous solid which crystallized from Et_2O to 3β,5,20ξ-trihydroxy-B-nor-5ξ-pregnane-6ξ-methanol 3-acetate α-tosylate (Vd) as needles, m.p. 153.5~154° (decomp.). $[\alpha]_D^{28}$ +45.1° (c=1.91). *Anal.* Calcd. for $C_{30}H_{44}O_7S \cdot \frac{1}{2}H_2O$: C, 64.70; H, 8.09. Found: C, 64.43; H, 8.36.

6β-Methyl-B-nor-5β-pregnane-3β,5,20β-triol (VId)——A solution of 1.1 g. of (Vd) dissolved in 70 cc. of dehyd. Et_2O was added dropwise into a suspension of 300 mg. of $LiAlH_4$ in 100 cc. of dehyd. Et_2O with stirring and the mixture was refluxed for 21 hr. When cooled, excess reagent was decomposed by addition of AcOEt, Et_2O layer was separated, and washed with H_2O and 2% $NaHCO_3$. After drying over Na_2SO_4, Et_2O was evaporated and 670 mg. of an amorphous solid residue thereby obtained was dissolved in benzene. When allowed to stand for some time, this crystallized into 374 mg. of cubic crystals, m.p. 176~178°, and recrystallized from benzene to 6ξ-methyl-B-nor-5β-pregnane-3β,5,20β-triol (VId), m.p. 182~184°. $[\alpha]_D^{29.5}$ +43.9° (c=2.40). *Anal.* Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.07; H, 10.43.

6β-Methyl-B-nor-5β-pregnane-3β,5,20β-triol 3,20-Diacetate——A solution of 130 mg. of (VId) dissolved in 2 cc. of pyridine and added with 1 cc. of Ac_2O was allowed to stand for 20 hr. at room temperature, poured into ice water, and extracted with Et_2O. The extract was washed consecutively with dil. HCl, dil. $NaHCO_3$, and H_2O, dried over Na_2SO_4, and Et_2O was evaporated in a reduced pressure, leaving 169 mg. of a colorless syrupy substance. This residue was dissolved in hexane and allowed to stand from which 6β-methyl-B-nor-5β-pregnane-3β,5,20β-triol 3,20-diacetate was obtained as needles, m.p. 101~102°. *Anal.* Calcd. for $C_{25}H_{40}O_5$: C, 71,39; H, 9.59. Found: C, 71.41; H, 9.47.

6β-Methyl-5-hydroxy-B-nor-5β-pregnane-3,20-dione (VIIb)——A solution of 300 mg. of CrO_3 dissolved in 10 cc. of 95% AcOH was added to a solution of 320 mg. of (VId) dissolved in 20 cc. of AcOH with ice cooling and the mixture was allowed to stand for 3 hr. at room temperature. Excess of the reagent was decomposed with MeOH, majority of the solvent was evaporated, the residue was diluted with H_2O, and extracted with Et_2O. The extract was washed with 2% $NaHCO_3$ and H_2O, dried over Na_2SO_4, and Et_2O was evaporated. The white residual solid was dissolved in benzene-$CHCl_3$ (9:1) mixture and chromatographed over 10 g. of alumina (Woelm grade II). Fractions eluted with benzene-$CHCl_3$ (9:1 and 4:1) afforded 183 mg. of white solid which recrystallized from benzene-hexane mixture to 6ξ-methyl-5-hydroxy-B-nor-5ξ-pregnane-3,20-dione (VIIb), m.p. 193.5~194°. $[\alpha]_D^{28}$ +57.4° (c=1.21). *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.75; H, 9.05. IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1710 (3-CO and 20-CO).

6ξ-Methyl-B-norpregn-4-ene-3,20-dione (VIIIb)——To a solution of 300 mg. of (VIIb) dissolved in 4 cc. of pyridine, chilled to 0°, 0.25 cc. of $SOCl_2$ was added dropwise with stirring, the mixture was allowed to stand at 0° for 10 min., and poured into ice water. This was extracted with E_2O, the extract solution washed consecutively with dil. HCl, dil. $NaHCO_3$, and H_2O, dried over Na_2SO_4, and Et_2O was evaporated to leave 320 mg. of pale yellow oily substance. This oily residue was chromatographed over 9 g. of alumina (Woelm grade II) and elution with benzene-hexane (1:1) mixture gave 87 mg. of a colorless syrupy substance. Recrystallization from hexane afforded 6ξ-methyl-B-norpregn-4-ene-3,20-dione (VIIIb), m.p. 112~113.5°. $[\alpha]_D^{28}$ +81.6° (c=2.53). *Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.62; H, 9.19. UV: λ_{max}^{EtOH} 240 mμ (ε 16,320). IR ν_{max}^{KBr} cm^{-1}: 1710 (20-CO), 1663, 1640 (4-en-3-one).

B-Norandrostane Series

Ozone Oxidation of Androst-5-ene-3β,17β-diol Diacetate (Ic)——A solution of 10 g. of (Ic) dissolved in 1000 cc. of CH_2Cl_2 was chilled to −60° to −70° with dry ice-Me_2CO and air containing O_3 (0.6 mmoles O_3) was introduced through the solution until the solution acquired bluish viole color. A mixture of 20 g. of Zn dust and 80 cc. of AcOH was added to this solution and the mixture was stirred for ca. 4 hr. at room temperature until the mixture became negative to KI reaction. Inorganic matter

was filtered off, the filtrate was washed four times with H_2O, dried over Na_2SO_4, and the solvent was evaporated in a reduced pressure below 40°. The colorless oily residue (11.29 g.) thereby obtained was chromatographed over 500 g. of alumina (Woelm grade III) and the column was eluted consecutively with benzene and benzene-$CHCl_3$ (19:1, 17:3, and 3:1) mixtures. The fractions eluted with benzene-$CHCl_3$ (17:3 and 3:1) mixtures afforded a substance of m.p. 173~179° (decomp.), which recrystallized from benzene-hexane to 3β,5,17β-trihydroxy-B-nor-5β-androstane-6β-carboxaldehyde 3,17-diacetate (IIIc) as cubic crystals, m.p. 177~179° (decomp.). $[\alpha]_D^{28.5}$ + 44.7° (c=2.33). *Anal.* Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.98; H, 8.36. IR ν_{max}^{Nujol} cm^{-1}: 3530 (OH), 2770 (CHO), 1740 (AcO), 1720 (CHO).

3β,5,17β-Trihydroxy-B-nor-5β-androstane-6β-methanol 3,17-Diacetate (IVc)——A solution of 2.0 g. of $NaBH_4$ in 100 cc. of 95% MeOH was added to 5.0 g. of (IIIc) dissolved in 200 cc. of MeOH, the mixture was stirred for 1 hr. at room temperature, 8 cc. of AcOH was added to decompose the excess reagent, and the solvent was evaporated in a reduced pressure. The residue was diluted with H_2O, extracted with Et_2O, and the extract was washed with H_2O. After drying over Na_2SO_4, Et_2O was evaporated in a reduced pressure and 4.85 g. (96.6%) of a white crystalline residue, m.p. 165~171°, was obtained. This was recrystallized from benzene-hexane mixture to 3β,5,17β-trihydroxy-B-nor-5β-androstane-6β-methanol 3,17-diacetate (IVc) as cubic crystals, m.p. 176.5~177.5°. $[\alpha]_D^{27}$ +58.0° (c=2.11). *Anal.* Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.72; H, 8.43. IR ν_{max}^{Nujol} cm^{-1}: 3480~3350 (OH), 1740, 1733 (AcO).

3β,5,17β-Trihydroxy-B-nor-5β-androstane-6β-methanol α,3,17-Triacetate——A solution of 200 mg. of (IVc) dissolved in 2 cc. of pyridine and added with 1 cc. of Ac_2O was allowed to stand for 20 hr. at room temperature, poured into ice water, and extracted with Et_2O. The extract was washed consecutively with dil. HCl, dil. $NaHCO_3$, and H_2O, dried over Na_2SO_4, and Et_2O was evaporated. The white crystalline residue, m.p. 120~121°, was recrystallized from benzene-hexane to 3β,5,17β-trihydroxy-B-nor-5β-androstane-6β-methanol α,3,17-triacetate, m.p. 122~123°. $[\alpha]_D^{28.5}$ +41.4° (c=2.10). *Anal.* Calcd. for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.82; H, 8.41.

3β,5,17β-Trihydroxy-B-nor-5β-androstane-6β-methanol 3,17-Diacetate α-Tosylate (Vc)——A solution of 1.8 g. of tosyl chloride dissolved in 20 cc. of pyridine was added to 3.5 g. of (IVc) dissolved in 50 cc. of pyridine and the mixture was allowed to stand for 20 hr. at room temperature. This was poured into ice water, extracted with Et_2O, the extract was washed consecutively with dil. HCl, dil. $NaHCO_3$, and H_2O, and dried over Na_2SO_4. Evaporation of Et_2O in a reduced pressure left 4.20 g. of a colorless syrupy substance, which was dissolved in Et_2O and the solution was allowed to stand. The crystals thereby obtained were recrystallized from Et_2O to 3β,5,17β-trihydroxy-B-nor-5β-androstane-6β-methanol 3,17-diacetate α-tosylate (Vc), m.p. 143~144°. $[\alpha]_D^{18}$ + 46.0° (c=2.55). *Anal.* Calcd. for $C_{30}H_{42}O_8S$: C, 64.04; H, 7.52. Found: C, 64.23; H, 7.58.

6β-Methyl-B-nor-5β-androstane-3β,5,17β-triol (VIe)——A solution of 5.76 g. of (Vc) dissolved in 110 cc. of dehyd. Et_2O was added dropwise into a suspension of 1.4 g. of $LiAlH_4$ in 140 cc. of dehyd. Et_2O, the mixture was refluxed for 21 hr., and cooled. AcOEt was added to decompose excess reagent, the mixture was acidified with dil. HCl, and Et_2O layer was separated. This was washed with H_2O, 2% $NaHCO_3$, and H_2O, dried over Na_2SO_4, and evaporation of Et_2O in a reduced pressure left 2.451 g. of a colorless oily substance. This residue was dissolved in benzene-$CHCl_3$ (2:1) mixture and chromatographed over 75 g. of alumina (Woelm grade II). The column was eluted with benzene-$CHCl_3$ (2:1 and 1:1) mixtures and the fraction eluted with 1:1 mixture of benzene and $CHCl_3$ afforded 1.747 g. (55.3%) of 6β-methyl-B-nor-5β-androstane-3β,5,17β-triol (VIe), which recrystallized from Me_2CO-H_2O to needles, m.p. 92.5~94°. $[\alpha]_D^{29.5}$ +42.6° (c=1.03). *Anal.* Calcd. for $C_{19}H_{32}O_3 \cdot 1\frac{1}{2}H_2O$: C, 68.06; H, 10.45. Found: C, 68.50; H, 1014.

6β-Methyl-5-hydroxy-B-nor-5β-androstane-3,17-dione (VIIf)——To a solution of 1.104 g. of (VIe) dissolved in 25 cc. of AcOH, cooled with ice, a solution of 2.2 g. of $Na_2Cr_2O_7 \cdot 2H_2O$ dissolved in 25 cc. of 95% AcOH was added dropwise, the mixture was allowed to stand for 4.5 hr. at room temperature, and MeOH was added to decompose the excess reagent. Majority of the solvent was evaporated in a reduced pressure, the residue was diluted with H_2O, and extracted with CH_2Cl_2. The extract was washed with H_2O, dil. $NaHCO_3$, and H_2O, dried over Na_2SO_4, and CH_2Cl_2 was evaporated, leaving 840 mg. of a crystalline substance. This residue was dissolved in benzene-$CHCl_3$ (4:1) mixture, chromatographed over 30 g. of alumina (Woelm grade II), and the eluate of benzene-$CHCl_3$ (4:1) gave 644 mg. (58.6%) of 6β-methyl-5-hydroxy-B-nor-5β-androstane-3,17-dione (VIIf), which recrystallized from benzene-hexane to needles, m.p. 187~189°. $[\alpha]_D^{27.5}$ +75.3° (c=1.82). *Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.71; H, 9.16. IR ν_{max}^{KBr} cm^{-1}: 3480 (OH), 1740 (17-CO), 1710 (3-CO).

6ξ-Methyl-B-norandrost-4-ene-3,17-dione (VIIIf)——To a solution of 250 mg. of (VIIf) dissolved in 3.3 cc. of pyridine and chilled to 0°, 0.21 cc. of $SOCl_2$ was added dropwise, the mixture was maintained at 0° for 10 min., and poured into ice water. This was extracted with Et_2O, the extract was washed consecutively with dil. HCl, dil. $NaHCO_3$, and H_2O, dried over Na_2SO_4. Evaporation of Et_2O

in a reduced pressure left 115 mg. of pale yellowoily sb nstance which was dissolved in benzene-hexane (1:1) mixture and chromatographed over 5.0 g. of alumina (Woelm grade II). The fraction eluted with benzene-$CHCl_3$ (1:1) mixture and benzene afforded 79 mg. of a crystalline substance which recrystallized form benzene-hexane to cubic crystals, m.p. 133.5~134°, of 6ξ-methyl-B-norandrost-4-ene-3,17-dione (VIIIf), $[\alpha]_D^{28.5}$ +90.6° (c=2.23). *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.46; H, 9.00. UV: λ_{max}^{EtOH} 239.5 mμ (ε 15,920). IR ν_{max}^{KBr} cm^{-1}: 1738 (17-CO), 1663, 1635 (Δ^4-3-CO).

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Summary

3β,5-Dihydroxy-6β-formyl-B-nor-5β-steroids (IIIa, b, c) of cholestane, pregnane, and androstane series were converted into the corresponding 3β,5-dihydroxy-6β-methyl-B-nor-5β-steroids (VIa, d, e) by reduction of (III) with sodium borohydride, followed by tosylation of 6-hydroxymethyl group and subsequent treatment with lithium aluminium hydride. The compounds (VI) were oxidized to 3-oxo-5-hydroxy-6β-methyl-B-nor-5β-steroid derivatives (VIIa, b, f) which were then dehydrated to 6ξ-methyl-B-norcholest-4-en-3-one (VIIIa), 6ξ-methyl-B-norpregn-4-ene-3,20-dione (VIIIb), and 6ξ-methyl-B-norandrost-4-ene-3,17-dione (VIIIf).

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71. Rinji Takasaki: Steroid Series. VIII.*1 Ozonization of Some Unsaturated Steroid Derivatives.

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In a previous paper of this series,[1] it was shown that cyclic ethylene acetals of cholest-4-en-3-one, pregn-4-ene-3,20-dione, and androst-4-ene-3,17-dione afforded the corresponding 5β,6β-epoxide in 53.5%, 55.5%, and 40.3% yield, respectively, together with 5-hydroxy-6β-formyl-B-nor-5β-steroid derivatives on ozonization and subsequent reduction of the ozonide followed by alumina chromatography.

Peracid oxidations of these steroid compounds are known to afford predominantly α-epoxides, along with a smaller amount of the β-epimers. The formation of epoxide by the action of ozone on an ethylenic linkage has sometimes been recognized when the double bond is sterically hindered on one side.[2] It should be noted, however, that epoxidation reaction proceeded selectively to form the β-epimer with ozone, in contrast to the peracid oxidation of the unsaturated steroid compounds. Early reports suggest that catalytic hydrogenation of 3-oxo-Δ^4-steroid generally affords 3-oxo-5β-*H*-steroid, while 5α-*H*-epimer is obtained, clearly due to the steric environment, when it possesses

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*1 Part VII. : This Bulletin, **10**, 439 (1962).

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